THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.[1]

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In order to discuss treatment of syphilis of the central nervous system it is essential to orient ourselves in the various problems which this disease presents.

It is now well established that spirochetes circulate in the blood of practically all patients in the late primary and early secondary stages, and during this period the central nervous system is frequently involved. In fact, with the early and almost universal dissemination of the infectious agent it is difficult to conceive how any organ escapes infection. It is not alone the presence of the spirochetes, but the reaction of the tissues toward them which determines the type of infection. It is recognized that spirochetes can lie dormant in the tissues, in latent cases, with practically no cellular reaction about them. Different observers report wide variation in the relative frequency with which the cerebrospinal fluid shows evidence of alteration in the secoodary period. Ravaut[2] found abnormalities, with pleocytosis or globulin excess, or both, in 67 per cent. of cases, Altmann and Dreyfus[3] in 66 per cent. Gennerich[4] states that at some time, either before or during intensive salvarsan treatment, 90 per cent. of his cases in the secondary period showed some abnormality of the cerebrospinal fluid. Ellis and I[5] found only 33 per cent. of abnormal fluids in untreated patients in the secondary period, but had the fluids in all patients in the secondary period been included in our statistics the percentage would be somewhat higher.

From the above observations it is evident that infection of the central nervous system occurs in a large proportion of cases of secondary syphilis. Since we know that only a small proportion of syphilitic patients show nervous involvement in later years it is evident that in many cases this infection must undergo spontaneous resolution. This phenomenon corresponds with the course of syphilis elsewhere in the body, and is probably due, in part, to a tissue immunity which develops as a result of prolonged contact between parasite and host. As a result of this tissue immunity the secondary eruption disappears, and cutaneous relapses may never recur even in untreated patients. If, however, cutaneous manifes-

[1] Read at the Tenth Triennial Session of the Congress of American Physicians and Surgeons, Washington, May 9, 1916.
[2] Ann. de dermat. et de Syph., 1903, S. 4, iv, 1.
[3] München. med. Wchnschr., 1913, lx, 404.
[4] Die Liquorveränderungen in dem einzelnen Studien der Syphilis, Berlin, 1913.
[5] Jour. Exp. Med., 1913, xviii, 162.

tations do recur they become more and more localized, tend to group, and to involve deeper structures, with finally gummatous changes.

A similar process appears to occur in the central nervous system. Following the initial inflammation the organisms deposited in the meninges during the period of spirochetemia are usually destroyed; but in some cases they remain latent only to become active after a period of months or years. This is the usual course of syphilitic infection in untreated or poorly treated cases. The character of the picture may, however, be altered by the institution of intensive treatment. It has long been observed that cases of primary syphilis, relapsing after unsuccessful attempts at abortive treatment with mercury, are liable to show severe skin lesions. Similar deep nodular or ulcerative lesions are frequently seen in the relapses following inadequate salvarsan treatment. This phenomenon of increased severity noted in relapsing lesions of the skin occurs also in the central nervous system, and explains the occurrence of meningitis with cranial nerve paralysis in many of the inadequately treated cases of secondary syphilis. In these patients the greater part of the infecting organisms have been destroyed by the remarkable spirocheticidal action of salvarsan. This has, moreover, been accomplished so rapidly that the usual tissue immunity which develops as a result of prolonged contact between parasite and host is lacking. As a result a small focus of spirochetes, tucked away safely in the tissues of the central nervous system, and thus escaping the spirocheticidal action of the salvarsan can develop in the susceptible host with great rapidity and severity. The severity of the meningitis is evidenced by the cerebrospinal fluid, which shows a marked pleocytosis, considerable globulin excess, and usually a strongly positive Wassermann reaction. The Wassermann reaction in the blood is frequently negative, showing how well the active syphilis is limited to the central nervous system. The failure to recognize this possibility of active meningitis in the early stages of syphilis, with a negative Wassermann reaction in the blood, may result in the failure to resume treatment at a most critical period. It should be emphasized that the development of this condition is due to inadequate intensive treatment, and that a few doses of salvarsan, without continued treatment, may result in more severe nervous manifestations than if milder therapy had been applied.

The recognition of the early involvement of the central nervous system is important not only because of the possibility of the development of an early meningitis but also from the stand-point of prophylaxis of the later and more destructive conditions. The best treatment of brain gummata, tabes, and paresis will always be their prevention.

Before starting treatment in any case it is well to try to recognize the character of the involvement, for the subsequent therapy is, to a certain extent, determined by the type of manifestation. These

manifestations depend upon the tissues involved, and upon the reaction of those tissues to the irritative effect of the spirochetes. The disease may implicate the meninges, bloodvessels, or parenchyma. While it is conceivable that any one of these structures may be affected alone, still the intimate relation of one structure to the other makes it almost impossible for one to be diseased without the others sharing to a certain extent in the pathological process. There is, however, a type of nervous disease due to syphilis in which the infection seems to involve the vessels in the form of an endarteritis. In this instance the cerebrospinal fluid shows little if any abnormality, and the symptoms are referable to the arterial sclerosis of the cerebral vessels rather than to actual interstitial or parenchymatous disease. The response of this type of case to treatment depends upon the extent to which the endarteritis can be favorably affected and not upon the resolution of a syphilitic exudate in the meninges.

Following the demonstration of the Treponema pallidum in paretic brains a new classification of lues of the brain and cord has arisen. This comprises (1) interstitial types, which include the lesions previously classified under cerebrospinal syphilis, and (2) parenchymatous types, which include paresis and tabes dorsalis.

In both the interstitial and parenchymatous forms the one common lesion is the perivascularitis which may vary, to a wide degree, from a simple mantling of the vessel to a collection of cells in the form of miliary gumma, and when combined with a similar process in the meninges may result in large gumma formation. In the interstitial forms, which include meningitis, meningo-arteritis, and gumma, the disturbance in function is due either to an actual destruction of the nervous elements or to a cutting off of nutrition to the nerve tracts and centers. This latter condition may be brought about by the narrowing of vessels and compromising of the lymphatic spaces to the edema surrounding active inflammation and to pressure from the tumors. In fact, the remarkable improvement of many of these cases under treatment can be explained only on the basis that the pathological process has been largely limited to the vessels and meninges. In the parenchymatous forms the outstanding picture is degeneration of nervous elements combined with symptoms of irritation of these structures. Unfortunately it is impossible to examine microscopically the tissues in these parenchymatous forms until late in the disease, when the degeneration is far advanced. But even at this time perivascularitis and focal meningitis are usually seen, and it does not seem unreasonable to consider that much of the degeneration is secondary to a disturbance of the nutrition of the cell or axis-cylinder, which has resulted from a blocking of the perivascular, perineural, or perineuronal lymph spaces by the cellular exudate.

In paresis the presence of the spirochete in the brain substance

may by the liberation of toxins result directly in the death of the cell. In tabes dorsalis, however, the active inflammatory process is not usually found in the most obviously degenerated areas, namely, the columns of Goll and Burdach, but rather in the dorsal roots and in the meninges surrounding them. An example of the earliest stages of tabes is the interesting case of Larkin[6] in a patient with "sciatica," girdle pains, pleocytosis, and positive Wassermann reaction in the cerebrospinal fluid, who died from a ruptured aortic aneurysm and whose postmortem showed insular sclerosis of the posterior nerve root, with accompanying syphilitic meningitis but no column degeneration.

From the examination of the retina and optic nerves of many cases of optic atrophy in tabetics and paretics, Stargardt[7] concluded that the atrophy is secondary to a round-cell infiltration of the intracranial portion of the optic nerve and the chiasm. In those cases with a segmental optic atrophy there was only a partial infiltration of the optic nerve. He argues against the view that tabetic optic atrophy is a system disease due to a toxin, but believes rather that it is an example of the reaction of the nervous tissue to the spirochete, for in several of his cases the auditory and olfactory nerves were similarly infiltrated. Spiller[8] showed that the essential lesion in tabetic oculomotor paralysis is due to a round-cell infiltration in the oculomotor nerves at their point of emergence from the medulla, which he thinks is probably secondary to the pial infiltration in this region. He considers that the nuclear degeneration is usually secondary to the inflammation of the nerve stem. Thus it appears that the classification of the various tabetic atrophies as primary is only an attempt to explain them in terms of the older opinion that these diseases were parasyphilitic in nature. As a matter of fact, they all appear to be secondary to a chronic syphilitic meningitis.

Chronicity is probably an important element in the development of parenchymatous syphilis. The outstanding symptoms of most cases of tabes or paresis develop from the tenth or twelfth year, after the primary infection. Upon careful questioning of many of these patients it will be found that some single symptom, such as pain or isolated nerve paralysis, often transitory in character, has occurred years previously, and their nature is often recognized only after the disease is well developed. These facts point to the probability that a low-grade inflammation with subsequent atrophy has been going on for years, and only after a sufficient number of tracts or centers are involved to interfere with the patient's usual activities does he seek the aid of the physician. On the other hand,

[6] Cited by J. A. Fordyce, Harvey Lectures, 1914–15, Series X.
[7] Allg. Ztschr. f. Psych., 1912, lxix, 735.
[8] Jour. Nerv. and Ment. Dis., 1915, xlii, 15.

the majority of cases of the interstitial type develop in the first three years after infection. The course is more rapid and the symptoms appear with greater violence, no doubt due to the fact that there is a more extensive and rapid development of the meningeal and perivascular exudate.

In both tabes and cerebrospinal syphilis, then, we are dealing with diseases of a similar nature. The variation in the manifestations seems to depend upon the difference in the rapidity and degree of development as well as upon the localization of the inflammatory process. In tabes the infiltration being less intensive and slower, the picture of degeneration is brought more vividly into the foreground. The spinal fluid in the two diseases is practically the same, even to the type of curve in the gold reaction. Both also respond to specific treatment in much the same manner, although at a different rate, and while the symptoms due to irritation are improved, those due to degeneration are little if any affected.

In paresis, on the other hand, we appear to be dealing with a disease which is not strictly comparable with the two just discussed. There are certain points of similarity, namely, in the meningitis and perivascularitis. The direct action of large masses of spirochetes in the substance of the cerebral cortex may possibly result directly in the destruction of cortical cells and fibers. The peculiar type of curve in the gold reaction, moreover, points to some essential difference between this disease and tabes. The difference in response to treatment is also most striking. While most cases of tabes will show the favorable influence of treatment both in the spinal fluid and in marked and persistent clinical improvement, the response of most paretics to a similar or more intensive treatment is much less noticable, and the ultimate results are usually discouraging. Whether this difference in response is due to difference in accessibility of the active lesion or to the fact that in paresis the disease attacks portions of the central nervous system, which are more essential to the orderly carrying on of vital functions, are questions which are as yet unanswered.

It goes without saying that the best preventive of syphilis of the central nervous system is the prophylaxis of syphilis; but this problem is far from solved. Next in importance is the proper treatment of syphilis in the early stages. It should be emphasized at this point that no case should be released from treatment until the cerebrospinal fluid has been shown to be normal, insofar as pleocytosis and Wassermann reaction are concerned. Whether a slight excess of globulin is an indication for continuation of treatment, if all other abnormal elements are absent, is still an open question. In a number of patients with meningitis in the secondary period, whom we have followed for several years, the globulin is still in excess, although all other evidence of the disease had been absent for three or more years.

Even with the present diagnostic methods and several effective therapeutic agents it is safe to say that a fair proportion of patients with syphilis are poorly treated, and probably a majority of them are released without lumbar punctures. The failure of many patients to be followed until cured is due to several causes: (1) the patients fail to realize the importance of proper treatment in the prophylaxis of later disease and discontinue their treatment of themselves; (2) there is still a surprising lack of facilities in dispensaries for the proper treatment of syphilis; (3) many physicians fail to realize the long systematic course that is required to eradicate the disease completely; (4) there are many cases of innocent syphilis and syphilis with slight, if any, early manifestations which go untreated and later develop serious nervous lesions. (Table I.)

TABLE I.

Mattauschek and Pilcz — Total cases 4134

Developed paralytica dementia	198 = 4.8 per cent.
" tabes dorsalis	113 = 2.7 "
" cerebrospinal lues	132 = 3.2 "
Total	443 = 10.5 "

EFFECT OF TREATMENT.

	None.	1 course.	Repeated energetic
Number of cases	100	134	924
Developed G. P.	25 = 25 per cent.	31 = 23.1 per cent.	30 = 3.2 per cent.
" tabes	11 = 11 "	16 = 11.9 "	25 = 2.7 "
" cerebrospinal lues	3 = 3 "	21 = 15.6 "	71 = 7.6 "

	Poorly treated 1880-84.	Better treated 1895-99.
Number of cases	617	1139
Developed G. P.	60 = 9.7 per cent.	37 = 3.2 per cent.
" tabes	22 = 3.5 "	16 = 1.4 "
" cerebrospinal lues	15 = 2.4 "	23 = 2.4 "

While the incidence of cerebrospinal involvement in syphilis varies in different races and in the different sexes the experiences of Mattauschek and Pilcz[9] is representative. These authors followed 4134 cases of syphilis in officers in the Austro-Hungarian army who were infected between 1880 and 1900. These cases were followed until 1912. The results of these investigations are shown in Table I. A striking feature of the table is the difference in the percentage of cases that developed tabes and paresis who were untreated or poorly treated compared with those who had been energetically treated. Practically a quarter of the poorly treated cases developed paresis contrasted with a little over 3 per cent. of those who were well treated. Similarly from 11 to 12 per cent. of the poorly treated ones developed tabes, while only a fifth of this proportion of well-treated patients developed this disease. A single course of treatment seemed to increase the liability to the cerebrospinal form of

[9] Ztschr. f. ges. Neur. and Psych., 1910-11, iv, orig., 697; 1913, xv, 608.

lues. This observation is of added interest in view of our present knowledge of the results of insufficient salvarsan treatment on the development of cerebrospinal syphilis already discussed in an early part of this paper. A similar parallelism between early efficient treatment and diminished incidence of tabes and paresis is seen in the last part of the table. In the period between 1880 and 1884 the treatment was relatively insufficient, while in the period between 1895 and 1899 there was an improvement in the general treatment of the disease with a corresponding decrease in the incidence of parasyphilis. It is striking that the incidence of cerebrospinal syphilis in the two groups is the same.

If the difference between poor application of mercury and fairly efficient application is so marked it is reasonable to expect that under the modern intensive treatment with both mercury and salvarsan the incidence of parasyphilis should be even more markedly reduced. From a simple, economic point of view the State should provide for the proper treatment of early syphilis, for upon the State eventually falls the cost of caring for the paretic and, to a less extent, for the tabetic.

From the standpoint of prophylaxis of tabes or paresis it is also important to realize that they frequently develop slowly, and that signs or symptoms are often present for years before the disease is fully manifest. Lately more attention has been directed to the monosymptomatic forms of syphilis of the central nervous system. Some authors claim that these forms are more frequent today than formerly, and that tabes is assuming a milder character; but it is more probable that their detection is due to refinement in diagnosis. While fairly numerous cases are reported in which the monosymptomatic forms remained free from further symptoms for many years in spite of lack of treatment it is wiser to regard all such cases as being early forms of late serious disease. Years ago Erb called attention to the importance of ophthalmoplegia interna as a forerunner of tabes or paresis and he has followed several cases from the appearance of a simple eye lesion to the fatal ending in paresis. Many patients with tabes give a history of a transitory squint which was present years before any other symptom. Often the condition has improved after the administration of a small amount of iodides or mercury and the patient has been allowed to escape from further observation. Auditory nerve lesions are also described early in tabes as well as in cerebrospinal syphilis. These patients usually consult the otologist. It is important for the specialist to realize that these isolated nerve lesions are a part of the general disease, syphilis of the central nervous system, and that they are usually manifestations of a basilar meningitis. Surgeons also see early manifestations in abdominal disturbances. Nuzum[10]

[10] Jour. Am. Med. Assn., 1916, lxvi, 482.

recently reported that among a thousand cases of tabes admitted to Cook County Hospital, 87 had previously undergone laparotomy because of the mistaken diagnosis of their abdominal pain. It is important to remember that gastric crises, either mild or severe, may be present as the first manifestation of tabes for years before full development of the disease. Other single symptoms which are often present for a longer or shorter period are bladder disturbances, lightning pains in the leg, and "rheumatism." The general practitioner or the specialist should recognize the nature of these symptoms and place the patient under proper treatment, for it cannot be emphasized too strongly that prevention of degeneration is worth vastly more than the treatment of symptoms once they have fully developed.

The examination of the blood and cerebrospinal fluid is of the greatest help in clearing up the diagnosis in doubtful cases, and to a certain extent in determining the type of syphilitic involvement of the central nervous system. While these examinations are of great value, they do not replace but only complement a careful clinical examination. I cannot do better than quote Miller:[1] "The value and interpretation of any laboratory method should always be based upon the most careful clinical study of the cases in which it is applied;" and also, "Any normal reaction in the cerebrospinal fluid may be present or absent in any luetic involvement of the brain or spinal cord." There are certain combinations of reactions which occur with sufficient frequency in certain conditions to render such findings highly significant. An increase in globulin is found in most cases of any type; it is most marked in paresis, but may be equally intense in secondary meningitis. Pleocytosis is usually the most intense in meningitis in the secondary stage, but counts above 100 are not infrequent in later cerebrospinal syphilis, tabes, and paresis. The type of curve given by the Lange gold reaction in cerebrospinal lues and tabes is of confirmatory value, but its great field of usefulness seems to be in differentiating paralytica dementia from these two conditions. The fact that the fluid from a patient with a clinical diagnosis of tabes, or cerebrospinal syphilis, gives a paretic curve does not militate against the reaction, for it is well known that between 10 and 15 per cent. of tabetics develop paresis, and at time it is impossible to differentiate between cerebral syphilis and paresis. If future observations confirm what now seems probable, namely, that a paretic curve obtained with the spinal fluid of patients clinically not paretic points to a possible development of this disease, it will be of importance in prognosis and of value in determining why symptoms of mental disorder appear in spite of vigorous and prolonged treatment.

At this point it is well to emphasize the value of constant methods

[1] New York State Jour. Med., 1915, xv, 376.

in making the various tests on the cerebrospinal fluids. Dilutions for cell counts should be made immediately. The necessity of proper solutions for the gold test have been pointed out by Miller[12] and his co-workers. Of no less importance is the titration of the strength of the Wassermann reaction in the spinal fluid. The designation of + + + + or negative Wassermann reaction in the fluid means but little unless we know the amount of fluid that was used in obtaining these readings. This is especially true when the effect of treatment is being estimated. For example, if 0.2 c.c. or 0.4 c.c. has been the only amount used to test the fluid a relatively mild treatment may change the reaction to negative. On the other hand, if only 1 c.c. has been used a more intensive treatment may not affect the reading, although, as a matter of fact, the reaction may be much weaker. The only way to judge accurately of the effect of treatment on the reaction is to test the fluid with diminishing amounts corresponding to values between 2 c.c. and 0.2 c.c. in the original Wassermann test (smaller amounts if necessary) and determine the point at which the reaction is completely positive. If, then, with a given amount of treatment the positive point has moved from 0.2 c.c. to 0.6 c.c. or higher, we know that the treatment is having some effect. This, of course, presupposes that constant methods are used at different times, for if a very sensitive method is used at one time and a comparatively unsensitive one at another the relative value of the two tests is lost.

The problem of treatment of syphilis of the central nervous system is complicated by the peculiarities of the subarachnoid space which, in addition to the larger spaces and cisterna, is directly continuous with the perivascular, perineural, and perineuronal lymph spaces. It does not seem unreasonable to suppose that the infection is carried by the cerebrospinal fluid along these channels, and the various meningeal and perivascular lesions can be most easily explained in this way. Frühwald and Zalozieckl,[13] in a review of their own cases and of the literature, have shown that the fluid is occasionally infectious in all stages from the secondary period to tabes and paresis.

The reaction to the spirochete is meningitis and perivascularitis. It is probable that the nerve cells and fibers obtain their nutrition to a considerable degree through these spaces, hence plugging of them with exudate not only compromises the nutrition of these structures but also probably increases the difficulties with which therapeutic agents are brought into contact with the exudate. At present it seems almost superfluous to recite the numerous experiments which prove the separateness of the subarachnoid space from the general lymphatic and blood-vascular systems. Antibacterial immune bodies, vital stains, and most drugs, when

[12] Johns Hopkins Hosp. Bull., 1915, xxv, 391.
[13] Berl. klin. Wchnschr., 1916, liii, 9.

administered by mouth or parenterally, do not reach the subarachnoid space in demonstrable quantities. It is true, however, that many drugs, given either by mouth or subcutaneously, do act on the central nervous system, but these drugs administered subdurally act in much smaller quantities. Many years ago Lewandowsky[14] showed that strychnin when injected intraspinally was ten times as effective as when injected intravenously. Similarly, sodium ferrocyanide subdurally was potent in one-hundredth the intravenous dose. The action of both drugs was at first local and then general, showing that they were rapidly diffused through the cerebrospinal fluid.

In many cases the general administration of mercury, iodides, and salvarsan affects favorably the course of syphilis of the cerebrospinal axis. This favorable influence is especially marked in the early forms of the disease. The tendency, however, of cerebrospinal syphilis to relapse in spite of energetic mercurial and iodide treatment has long been noted by syphilographers and neurologists, and the failure of most cases of tabes to respond to the antiluetic treatment of the presalvarsan era made therapeutic nihilists of most neurologists. Even the brilliant clinical improvement of most cases of cerebrospinal syphilis and tabes after salvarsan intravenously has not been followed by a parallel improvement in the cerebrospinal fluid. Dreyfus,[15] who gives courses of salvarsan of 4 to 6 gms. combined with ten to twelve injections of calomel or gray oil, notes that many such courses are necessary to eliminate all signs of the disease. In only 3 out of 125 cases of cerebrospinal syphilis did the fluid become normal after one or two courses. Gennerich,[16] who is famous for the intensity of his antisyphilitic treatment, says that he feels that all cases with meningeal involvement in any stage should have intraspinal treatment. Many observers report cases of cerebrospinal syphilis or tabes which, having come to a standstill, both clinically and pathologically, under general treatment, have shown renewed improvement under intraspinal therapy.

The desirability of subarachnoid therapy has been well established. The problem was to find some beneficial therapeutic substance which could be repeatedly introduced without injury to the delicate nervous tissue, for only by repeated and prolonged treatment can we hope to arrest any form of cerebrospinal lues permanently. Last year,[17] the writer reviewed the use of these various agents and the methods of their administration. Suffice it to say that the preparations which have stood the test of time are (1) the serum obtained from patients shortly after intravenous injections of

[14] Ztschr. f. klin. Med., 1900, xl, 480.
[15] München. med. Wchnschr., 1914, lxi, 525.
[16] Ibid., 1915, lxii, 1696.
[17] Swift, H. F., Jour. Am. Med. Assn., 1915, lxv, 209.

salvarsan; (2) serum to which small quantities of salvarsan have been added; (3) neosalvarsan in small quantities and weak concentration, and (4) mercurialized serum.

The direct application of mercury in the form of albuminate, as devised by Byrnes,[18] should theoretically be of value, and the reports seem to indicate that if the amount of mercury is kept under the irritating dose, beneficial results may be expected from its injection. It is well to call attention to the danger of repeated injections of mercurialized horse serum, which may lead not only to a general anaphylactic state to horse serum, but may cause the meninges to become hypersensitive to the foreign protein, and repeated injections over a number of months may lead to a chronic meningitis similar to the condition we are trying to combat.

The injection of neosalvarsan in concentrated solutions, as recommended by Ravaut,[19] or even in one pro mille solutions has been proved by numerous observers to be a dangerous procedure, since it is apt to be followed by various degrees of urinary retention and incontinence, rectal paralysis, paresthesia of the legs, ataxia and girdle sensations, and, in severe cases, by paralysis of the lower extremities and death. A given dose may be well tolerated several times, but later be followed by severe symptoms. Because of the uncertainty of unfavorable sequelæ, intraspinal injections of neosalvarsan should be given with extreme caution. Gennerich[20] lately reported that by using very dilute solutions he has been able to avoid these unpleasant symptoms. He, however, warns against the use of more than 0.5 mg. in spinal cord disease and not over 1 or 2 mg. in patients with paresis or syphilitic meningitis. Personally, I feel that repeated doses of this size are dangerous.

The addition of small quantities of salvarsan to serum as recommended by Ogilvie[21] was devised to give a known amount of salvarsan instead of the uncertain amounts in the serum salvarsanized *in vivo*. Marinesco and Minea[22] have noted that neosalvarsan is less irritating when diluted with serum than when dissolved in water or saline. Both Ogilvie and Fordyce,[23] however, have noted bladder disturbance and paresthesia in the legs when more than 1 mg. of salvarsan was added to the serum, and now I recommend that the dose should never be over 0.5 mg., usually less. With these quantities, intraspinal treatment has been followed by distinctly beneficial results.

The use of the serum of patients withdrawn after intravenous salvarsan injections has been criticized chiefly because of the small amounts of salvarsan it contained. We have found that the

[18] Swift, H. F., Jour. Am. Med. Assn., 1914, lxiii, 2182.
[19] Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, xxxvi, 752.
[20] Loc. cit.
[21] Jour. Am. Med. Assn., 1914, lxiii, 1936.
[22] Rev. neurol., 1914, xxii, 337.
[23] Jour. Am. Med. Assn., 1914, lxiii, 552.

majority of the sera one hour after an intravenous injection contained 0.01 mg. or more per cubic centimeter. When 12 to 20 c.c. of serum are used each treatment represents the injection of from 0.12 to 0.2 mg. of salvarsan. As above noted it is unsafe to inject intraspinally more than a fraction of 1 mg. of either salvarsan or neosalvarsan. The uncertainty of the dosage is an objection which cannot be overcome unless definite quantities of salvarsan are added.

The "autosalvarsanized serum" is, however, definitely spirocheticidal and the salvarsan is present in a colloidal combination with the serum which cannot be dialyzed through a celloidin membrane, as can salvarsan alone (Young,[24]). Salvarsan in this colloidal state is probably more slowly diffused out of the cerebrospinal fluid, hence is longer in contact with the syphilitic exudates. Moreover it seems to us that some of the beneficial effect from serum injection may be due to the introduction of the serum *per se*, for[25] we have obtained very interesting results from the intraspinal injection of non-salvarsanized both in diminishing pleocytosis and strength of the Wassermann reaction. The amount of the diminution in the Wassermann reaction is shown graphically in Table II. By reading from above downward the initial strength of the Wassermann reaction is indicated, while the reading from left to right gives the strength after treatment. The original strength of the reaction is also indicated by the heavy blocks. The number of treatments is indicated in parenthesis. It will be seen that 7 out of the 8 cases showed a diminution in the strength of the reaction, and in 3 of them it became negative with 1 c.c. fluid. During the period of observation none of the patients received any other treatment. If two of the cases, *A* and *B*, in which there was little or no effect, the treatment was continued with "autosalvarsanized serum," from other patients, with more marked diminution in the strength of the reaction, as is shown in part two of the chart. The severity of the infection in one of these cases is indicated by the fact that ten months' intravenous and intraspinal treatment was required before the reaction became completely negative. Four other patients were treated with intraspinal injections of salvarsanized serum, and in three of these the reaction became negative with 1 c.c. fluid. A résumé of the results in these 12 cases, treated only intraspinally with either normal or salvarsanized serum, shows that in half of them the reaction became negative with 1 c.c. of fluid, and in the others there was distinct diminution in the strength of the reaction. Two of these patients with gastric crises, Argyl-Robertson pupils, loss of tendon reflexes, bands of cutaneous anesthesia, and loss of deep pain sensation have been observed

[24] Biochem. Jour., 1915, ix, 479.

[25] The cases reported in this and subsequent tables were treated at the Rockefeller Hospital in collaboration with Drs. Ellis, Chesney and Stillman. A number of them were followed at the Presbyterian Hospital.

for over three years without any return of their trouble, and the fluids have remained normal. The results in these cases seem to prove that benefit is derived from intraspinal injections of serum. The explanation of these effects may be and probably is theoretical, but so are the objections to the treatment. The experimental facts stand and the injection of autosalvarsanized serum is followed by fewer permanent unpleasant effects than result from the intraspinal injection of any other antisyphilitic remedy.

TABLE II.—EFFECT OF INTRASPINAL INJECTIONS ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

Non-salvarsanized Serum.

W. R. before treatment.	W. R. after treatment.								No. of injections.
	++++					−−	++++	−−	
	0.2 c.c.	0.4	0.6	0.8	0.1	0.1	2.0	2.0	
0.2 c.c.		1 A	....	....	....	....	....	....	8
0.4 c.c.	....	1 B	....	....	....	....	....	....	7
0.4 c.c.	....		1	....	....	....	....	....	12
0.4 c.c.	....	....	....	....	1	....	....	....	12
0.6 c.c.	....	....		1	....	....	....	....	4
0.6 c.c.	....	....		....	....	1	1	....	17
0.6 c.c.	....	....	....	....	....	1	....	1	6
1.0 c.c.	....	....	....	....		1	....	....	6
Total 8	....	2	1	1	1	3			

Salvarsanized Serum.

W. R. before treatment.	W. R. after treatment.								No. of injections.
	++++					−−	++++	−−	
	0.2 c.c.	0.4	0.6	0.8	1.0	1.0	2.0	2.0	
0.2 c.c.		....	1	....	....	....	....	....	12
0.2 c.c.		....	....	....	....	1	....	....	11
0.2 c.c.		....	....	....	....	1	....	....	4
0.4 c.c.	....		1 A	....	....	....	....	....	4
0.4 c.c.	....		....	1 B	....	....	....	....	8
0.6 c.c.	....	....		....	....	1	....	....	8
Total 6	....	....	2	1	....	3			

In some patients the pain which follows the injection is so severe that the treatments must be discontinued, but such instances are the exception. The willingness of most patients to return for treatments over long periods is sufficient proof that the method is not too unpleasant for practical application.

A word as to technic: In most of our work at the Rockefeller Hospital the blood was withdrawn one hour after intravenous treatment and the serum diluted to 40 or 50 per cent. with normal saline and injected in quantities of 30 to 40 c.c. of this dilution. It was thought that the dilute serum was less irritating, but for the past two years at the Presbyterian Hospital we have bled the

patient one-half hour after intravenous treatment and injected 15 c.c. of whole heated serum without any more reaction than with the older method. Most of the patients now receive both the intravenous and intraspinal injections on the same day and return to their usual occupations the following day. In this way a minimum of time is required. It is necessary to keep some patients in bed for longer periods. In such instances we try to give the treatments on Saturdays so that the patients may be in condition to work by Monday morning.

It has seemed to us that the treatments are better borne if not repeated oftener than once in two weeks. This is especially true in tabetics or patients with spinal syphilis. In paretics or patients with cerebral syphilis the intervals may be shorter. At times it seems wiser to lengthen the intervals. It is well to bear in mind that a certain amount of irritation always follows the introduction of any foreign substance into the subarachnoid space, and the effect of this should be allowed to disappear before the treatment is repeated. A good rule to follow in any form of treatment of cerebrospinal syphilis is not to push the treatment so hard that the patient's general health is depressed. With each treatment there should be some improvement in the general condition; at least there should be no regression; for if a depressing treatment is repeatedly added to a more and more depressed condition the ultimate effect will be injurious rather than beneficial.

The treatment of the several forms of syphilis of the central nervous system presents different problems according to the stage of the disease and the individual patient. One general principle which should always be considered is that in any patient who shows evidence of involvement of the cerebral meninges or brain, salvarsan treatment should be preceded by a short course of mercury to prevent the possible occurrence of a Herxheimer reaction in the region of vital nervous centers. Fortunately such distressing reactions are rare, and can be obviated by proper preliminary treatment. If the presence of gummata is suspected a vigorous course of potassium iodide is often followed by marked improvement. It has seemed to us that the response of cases in the tertiary stage to salvarsan has been more marked and lasting if the courses of salvarsan have followed treatment with mercury and iodides. Gummatous exudates resolve under this preliminary treatment and the spirocheticidal effect of the salvarsan is more readily brought into play.

In the meningitis of the secondary period the response to alternate courses of salvarsan and mercury has been prompt and permanent in all of our cases. Gennerich[25] is of the opinion that all these cases respond more rapidly to combined intravenous and intraspinal

[25] Loc. cit.

therapy, and advises giving two intraspinal treatments after the cerebrospinal fluid has become normal. Following any form of treatment in this condition the cerebrospinal fluid should be examined in two or three months after treatment has been stopped, and every six months for two or more years thereafter to forestall relapses.

In the tertiary forms of the disease the so-called interstitial forms, alternate courses of mercury and iodides, and of salvarsan are usually followed by decided improvement, both clinical and in the condition of the cerebrospinal fluid. If possible the fluid should be examined after each course or each pair of courses. Not infrequently it will be found that the fluid has become normal after a few months' treatment. If so the prognosis is good and treatment should be conducted along general lines. On the other hand if the strength of the Wassermann reaction is the same or only slightly altered after four to six months of intensive general treatment it may be well to resort to intraspinal therapy.

In tabes dorsalis, because of the apparent sensitiveness of many cases to mercury, it is better to start the treatment with small intravenous doses of salvarsan, gradually increasing and giving a treatment every week for a course of six to eight injections. If at the end of this course the Wassermann reaction in the fluid is considerably weaker a course of mercury may be tried, followed by another course of salvarsan, alternate courses being given with periods of rest until the fluid is brought to normal.[37] Many cases will be found, however, in which the strength of the reaction is only slightly altered by such a plan of treatment. The substitution of combined intraspinal and intravenous therapy in these patients will usually result in an improvement in the condition of the fluid. I am convinced that our aim should be to bring the fluids to normal and keep them there if we intend to speak of a cure of the syphilis. That this can be done in a majority of instances is shown in Table III, which gives the results in 37 cases followed for several years. All but 3 of these were tabetics, most of them well advanced. One was a case of diffuse myelitis, one of radiculitis, and one of opthalmoplegia interna. The cases are arranged in groups according to the original strength of the Wassermann reactions in the fluid, and the last finding is indicated in the vertical columns. In 30 of the cases (81 per cent.), the reaction became negative with 1 c.c. of fluid, but in 2 of these the reaction later increased in strength so that the final readings give 28 (75 per cent.) negative. Nineteen of these cases are also negative with 2 c.c., which is double the amount recommended by Hauptmann.[37] Of 18 cases which were negative with 1 c.c. or more, and have been followed from ten months to three and a half years without treatment, 14 remain

[37] München. med. Wchnschr., 1910, lvii, 1581.

negative with 2 c.c., 2 remain negative with 1 c.c., but positive with 2 c.c. One relapsed to positive with 1 c.c., and one with 0.6 c.c. In those cases in which the Wassermann reaction of the fluid increased in strength there was also a clinical relapse, while with a single exception in all the cases with persistent negative

TABLE III.—TABES DORSALIS. EFFECT OF TREATMENT ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

W. R. before treatment.	W. R. after treatment.									Amount of treatment.					
										Before W. R. neg. with 1 c.c., or until stopped.			Between neg. with 1 c.c. and neg. with 2 c.c. or until stopped.		
	++++					—	++++	—		Mos.	Int. ven.	Int. sp.	Mos.	Int. ven.	Int. sp.
	0.2 c.c.	0.4	0.6	0.8	1.0	1.0	2.0	2.0							
0.2 c.c.		1 ← ⓡ	..	..	..	..	....	..		12	16	12			
0.2 c.c.		..	1	..	..	..	....	..		7	..	12 ns			
0.2 c.c.		..	..	..	1	..	....	..		24	32	15			
0.2 c.c.		..	..	..	..	1	....	..		1	..	4 ss			
0.2 c.c.		..	..	..	..	1	....	1		4	..	11 ss			
0.2 c.c.		..	..	..	..	1 →	1 →	1		8	12	10	8	10	3
0.2 c.c.		..	..	..	..	1 →	1 →	1		13	16	16	3	4	4
0.4 c.c.	....		1	..	..	..	....	..		6	..	13 ns			
0.4 c.c.	....		..	1	..	..	....	..		8	15	11			
0.4 c.c.	....		1 ←		ⓡ	..	....	..		5	..	12 ns			
0.4 c.c.	....		..	..	..	1 →	1	..		11	21	7			
0.4 c.c.	....		..	..	..	1 →	1	..		15	24	18	4	6	5
0.4 c.c.	....		..	..	..	1 →	1	1		12	21	16	24	26	9
0.4 c.c.	....		..	..	..	1 →	1	1		29	35	18	8	8	
0.4 c.c.	....		..	..	..	1	....	1		14	3	2	cont.		
0.4 c.c.	....		..	..	..	1	....	1		12	14	11	cont.		
0.4 c.c.	....		..	..	..	1	....	1		17	14	29	cont.		
0.6 c.c.	....	..		..	1	ⓡ ←	ⓡ	..		6	11	8	8	13	1
0.6 c.c.	....	..		1		ⓡ		ⓡ		..	..	..	8	17	17
0.6 c.c.	....	..		..	..	1	....	..		5	..	8 ns			
0.6 c.c.	....	..		..	..	1 →	1	..		8	18	7	14	26	19
0.6 c.c.	....	..		..	..	1 →	1	..		12	22	16	2	2	2
0.6 c.c.	....	..		..	..	1 →	1	1		8	..	17 ns	9	17	16
0.6 c.c.	....	..		..	..	1 →	1	1		4	6	5	6	9	9
0.6 c.c.	....	..		..	..	1	....	1		2	..	6 ns	4	8	
0.6 c.c.	....	..		..	..	1	....	1		5	8	6	11	21	
0.6 a.c.	....	..		..	..	1	....	1		4	7	..	11	20	10
0.8 a.c.	....	..	..		1	..	....	..		2	5	4			
0.8 c.c.	....	..	..		..	1	....	..		11	15	9			
0.8 a.c.	....	..	..	..	..	1	....	1		12(3)	20	5			
0.8 c.c.	....	..	..	..	..	1	....	1		3	6	5	cont.		
1.0 c.c.	....	..	..	..	..	1	....	..		1	2	2			
1.0 c.c.	....	..	..	..	..	1	....	1		11	..	6 ns	cont.		
1.0 a.c.	....	..	..	..	..	1	....	1		1	2	2	cont.		
1.0 c.c.	....	..	..	..	..	1	ⓡ	1		1	3	2	cont.		
1.0 a.c.	....	..	..	..	..	....	....	1		..	2	1	cont.		
1.0 c.c.	....	..	..	..	..	1	....	1		11	..	6 ns			
37	....	1	3	2	3	25	4	19							
....	....	2.7%	8%	5.4%	8%	75%	....	49%							

ⓡ = relapse.
ns = normal serum alone.
ss = salvarsanized serum alone.

fluids the disease has not progressed. In this one patient, who showed advanced tabes on admission, there has been an extension of the area of cutaneous anesthesia, and a neuropathic arthropathy of the shoulder joint has developed in spite of a normal fluid and negative blood Wassermann reaction. It will also be seen that there is a certain correlation between the initial strength of the

Wassermann reaction and the amount of treatment which was given before it became negative with 1 c.c. The number of cases in some of the groups is too small for averages to be of value, but in general the 1 c.c. or 0.8 c.c. group required from one to three months, the 0.6 c.c. groups about six months, and the 0.4 c.c. and 0.2 c.c. groups about twelve months. Not infrequently an equal or greater amount of treatment was required to change the reaction from negative with 1 c.c. to negative with 2 c.c.

In the presence of a rapidly advancing case of tabes or of optic atrophy, where it is desirable to arrest the progress of the disease, in an important organ, the institution of combined intravenous and intraspinal therapy at the beginning should be seriously considered, as rapidity of cure is the end to be accomplished.

Compared with the results in other forms of lues of the central nervous system the treatment of paralytica dementia has been disappointing. With the proof of the active syphilitic nature of this disease it was thought that a cure might be expected from intensive treatment; but there is something in the nature of the disease which apparently prevents the remedies from reaching the spirochete in sufficient quantities to eradicate them completely. It is true that most of the cases improve clinically, and in some of them there is a marked improvement in the condition of the spinal fluid. Still, with corresponding amounts of treatment this response is much less marked than in tabes. In addition there is a decided tendency for pleocytosis and Wassermann reaction to increase in intensity when treatment is discontinued. In two of our patients (see Table IV) there was at first almost as marked clinical improvement and diminution in abnormal elements in the cerebrospinal fluid as is seen in tabes. Both have had two relapses, and with each relapse the response to treatment has been less marked. This indicates that as the paretic process grows older it is less amenable to treatment, and probably explains the difference in results from State hospitals for the care of the insane and those from private physicians. In State institutions the cases are usually much more advanced than those which come under the observation of private institutions or practitioners. Thus Runge[28] reports 37.4 per cent. remissions, Raecke[29] 55.4 per cent. improved on salvarsan intravenously, Cotton[30] with combined intravenous and intraspinal therapy 58 per cent. arrested or much improved, and Ogilvie[31] 34 per cent. with complete remissions and 40 per cent. incomplete remissions, a total of 74 per cent. improved. In 4 of Ogilvie's cases both the blood and spinal fluids were brought to normal. When we compare these results with the number of remissions in the presalvarsan

[28] Deutsch. med. Wchnschr., 1914, xl, 998.
[29] Ibid., 1913, xxxix, 1348.
[30] Am. Jour. Insanity, 1915, lxxii, 125.
[31] Jour. Nerv. and Ment. Dis., 1916, xlviii, 261.

era 5.7 per cent.[32] or 7.4 per cent.[33] the treatment of paretics seems justified. The return of a paretic to his business, even though it be for only six months or a year, is often of vital importance to his associates and family. Compared with our therapeutic efforts in chronic cardiac or renal disease the results obtained thus far in paresis are decidedly encouraging, although in none of these diseases can we speak of a cure.

TABLE IV.—PARALYTICA DEMENTIA. EFFECT OF TREATMENT ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

W. R. before treatment.	W. R. after treatment.							Amount of treatment.		
	++++					−	++++	Mos.	Int. ven.	Int. sp.
	0.1	0.2	0.4	0.6	1.0	1.0	2.0			
0.1 c.c.	1	....	....	....	....	....	....	23(6)	11	8
....	1	....	....	....	....	....	....	18	31	18
....	....	....	1	....	....	....	....	20	38	26
0.2 c.c.	....	....	....	1	....	....	....	14	24	24
0.4 c.c.	....	....	....	1	—⊖	....	....	36(11)	25	21
0.6 c.c.	....	....	....	1	——	——	—⊖	37	50	32

In the treatment of syphilis of the central nervous system we should never forget the patient, and that he may be suffering from disease of other vital organs. If there is marked ataxia, Fraenkel's reëducation movements are useful; if he is emaciated, attention should be directed toward diet and general nutrition. Most patients with this form of disease show a certain amount of mental abnormality. Here psychotherapy is of value. In other words, treatment must be individualized, and while a general plan should be followed in the various forms of the disease, each case may demand a certain deviation to meet the peculiar conditions.

The objects of therapy are threefold: (1) the cure of disease; (2) the amelioration of symptoms; (3) the prolongation of life. With the possible exception of paresis all of these objects may be attained in most cases of syphilis of the central nervous system. To be satisfied with the attainment of the last two without attempting to attain the first is to fail to apply all the means at our disposal.

[32] Runge, loc. cit.
[33] H. L. Paine, Boston Med. and Surg. Jour., 1913, clxviii, 681.